NDA 20-114

March 26, 1991	Wallace Laboratories submits NDA 20-114.
April 17, 1991	FDA acknowledges receipt of NDA 20-114 with receipt date of March 26, 1991.
June 25, 1991	Wallace Laboratories response to FDA request for information concerning Drug Master File reference letters.
August 2, 1991	Wallace Laboratories letter clarifying sites that will perform manufacturing, packaging, labeling and control operations.
August 8, 1991	Four month interim safety update submitted by Wallace Laboratories.
October 25, 1991	Wallace Laboratories response to FDA request for information concerning spray pumps used in the clinical trials.
December 16, 1991	Detailed safety update submitted by Wallace Laboratories.
December 19, 1991	Wallace Laboratories response to FDA request for information concerning labeling and study reports from clinical trials.
February 18, 1992	FDA not approvable letter detailing chemistry, manufacturing and control deficiencies in the application.
February 28, 1992	Wallace Laboratories letter declaring its intention to amend the application in response to FDA's February 18, 1992 letter.
February 28, 1992	Protocol for pharmacokinetic study in mice submitted for review (per FDA request) by Wallace Laboratories.
April 22, 1992	Response to FDA letter dated February 18, 1992 concerning pump use and patient compliance during clinical trials submitted by Wallace Laboratories.
May 4, 1992	Environmental Assessment Update submitted by Wallace Laboratories.
June 10, 1992	Full clinical study report for protocol 235 (per FDA request) submitted by Wallace Laboratories.
July 6, 1992	Wallace Laboratories letter clarifying contract packager/labeler of drug product.

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NDA 20-114

September 28, 1992	Item 9. Safety Update submitted by Wallace Laboratories.
October 23, 1992	Information concerning pharmacokinetics submitted by Wallace Laboratories.
November 2, 1992	Correction to information contained in submission dated June 10, 1992, submitted by Wallace Laboratories.
November 20, 1992	Data from pharmacokinetic study in mice submitted by Wallace Laboratories.
December 18, 1992	Response to FDA letter dated February 18, 1992 concerning chemistry, manufacturing and control issues submitted by Wallace Laboratories.
December 21, 1992	Full clinical report for protocol 195 concerning azelastine-alcohol interaction that was previously submitted to another azelastine NDA was incorporated by Wallace Laboratories into NDA 20-114 by cross-reference.
January 7, 1993	Full clinical report for NDA Study 24 concerning treatment of bronchial asthma that was previously submitted to another azelastine NDA was incorporated by Wallace Laboratories into NDA 20-114 by cross-reference.
February 19, 1993	Data re-analyses requested by FDA on November 5, 1992, submitted by Wallace Laboratories.
February 24, 1993	Patient distribution flow charts into controlled and uncontrolled clinical studies as requested by FDA submitted by Wallace Laboratories.
March 10, 1993	Desk copies of Volumes 1 (index) and 2 (summary) requested by Division of Scientific Investigation provided by Wallace Laboratories.
April 22, 1993	Minutes from a meeting on April 1, 1993, between FDA and Wallace Laboratories submitted by Wallace Laboratories.
May 7, 1993	Revised Environmental Assessment and freedom of information copy submitted by Wallace Laboratories.

NDA 20-114

May 17, 1993	Patient listings of adverse experiences and selected case report forms requested by Division of Scientific Investigation provided by Wallace Laboratories.
August 6, 1993	Data in response to FDA facsimile request for information dated May 21, 1993, concerning chemistry, manufacturing and control aspects submitted by Wallace Laboratories.
August 18, 1993	Data in response to FDA facsimile request for information dated June 1, 1993, concerning statistical analyses submitted by Wallace Laboratories.
August 24, 1993	Disassembled spray pump units requested by FDA submitted by Wallace Laboratories.
December 2, 1993	Archival volumes of NDA (previously stored by Wallace Laboratories at FDA's request) submitted by Wallace Laboratories.
January 13, 1994	FDA request for information concerning chemistry, manufacturing and control and environmental assessment issues.
February 16, 1994	FDA not approvable letter and request for information concerning clinical safety and effectiveness issues.
February 23, 1994	Wallace Laboratories letter notifying FDA of intent to amend the NDA in response to FDA's February 16, 1994 letter.
March 31, 1994	Wallace Laboratories letter confirming meeting for April 11, 1994, to address chemistry, manufacturing and control issues.
April 6, 1994	Data in response to FDA not approvable letter dated February 16, 1994, submitted by Wallace Laboratories.
May 10, 1994	Minutes from a meeting on April 11, 1994 between FDA and Wallace Laboratories submitted by Wallace Laboratories.
June 29, 1994	Additional data inadvertently omitted from the April 6, 1994 submission provided by Wallace Laboratories.
July 6, 1994	Wallace Laboratories letter confirming meeting with FDA to address clinical issues scheduled for July 27, 1994.

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NDA 20-114

July 7, 1994	Cardiac safety information submitted to another NDA incorporated by Wallace Laboratories into NDA 20-114 by cross-reference.
August 9, 1994	Wallace Laboratories letter summarizing understandings of cardiac safety data and analyses expected by FDA as a result of the July 27, 1994 meeting.
October 28, 1994	Data addressing cardiac safety issues addressed by FDA in the not approvable letter dated February 16, 1994, and at the July 27, 1994 FDA-Wallace Laboratories meeting submitted by Wallace Laboratories.
June 30, 1995	Data addressing chemistry, manufacturing and control issues contained in FDA's letter dated January 13, 1994, submitted by Wallace Laboratories.
June 30, 1995	Data addressing clinical issues contained in FDA's not approvable letter dated February 16, 1994, submitted by Wallace Laboratories.
August 2, 1995	Additional data inadvertently omitted from the June 30, 1995 clinical submission provided by Wallace Laboratories.
August 10/11, 1995	Desk copies of selected volumes from the June 30, 1995 clinical submission provided by Wallace Laboratories.
August 31, 1995	Extractable specification data in response to FDA's letter dated January 13, 1994, submitted by Wallace Laboratories.
September 8, 1995	Tabular adverse experience data from US and European controlled clinical trials in response to FDA request on August 22, 1995, submitted by Wallace Laboratories.
September 19, 1995	Gender efficacy analysis in response to FDA request on September 15, 1995, submitted by Wallace Laboratories.
September 22, 1995	Revised annotated labeling and diskettes submitted by Wallace Laboratories.
September 29, 1995	Revised environmental assessment in response to FDA request dated September 12, 1995, submitted by Wallace Laboratories.

NDA 20-114

October 5, 1995	Information brochure for distribution to the Pulmonary-Allergy Drugs Advisory Committee provided to FDA by Wallace Laboratories.
October 16, 1995	FDA letter notifying Wallace Laboratories of change in nomenclature for Astelin Nasal Spray.
October 30, 1995	Slides for use by Wallace Laboratories at the November 17, 1995 Pulmonary-Allergy Drugs Advisory Committee Meeting provided to FDA by Wallace Laboratories.
November 9, 1995	Revised slides for November 17, 1995 meeting provided to FDA by Wallace Laboratories.
December 29, 1995	FDA approvable letter for NDA 20-114 issued.
January 2, 1996	Wallace Laboratories letter advising FDA that it intends to amend the NDA in response to the December 29, 1995 approvable letter.
March 25, 1996	Wallace Laboratories letter requesting a meeting to discuss labeling for pediatric patients less than 12 years of age in accordance with the pediatric rule published in the Federal Register.
May 8, 1996	Documentation to support a meeting request on pediatric labeling submitted by Wallace Laboratories.
May 13, 1996	Data addressing chemistry, manufacturing and control issues addressed in FDA's approvable letter dated December 29, 1995, submitted by Wallace Laboratories.
May 22, 1996	FDA letter declining meeting on pediatric labeling and outlining deficiencies in available data.
June 7, 1996	Data addressing nitrosamines and specifications submitted by Wallace Laboratories.
July 3, 1996	Wallace Laboratories telephone facsimile addressing clarifications to chemistry, manufacturing and control data.
July 8, 1996	Wallace Laboratories telephone facsimile addressing clarifications to chemistry, manufacturing and control data.

NDA 20-114

July 10, 1996	Data submitted by Wallace Laboratories formalizing telephone facsimiles of July 3 and 8, 1996.
July 17, 1996	Meeting request to finalize chemistry, manufacturing and control sections of application submitted by Wallace Laboratories; request withdrawn by Wallace Laboratories on July 24, 1996 at FDA request.
July 19, 1996	Meeting request to finalize product labeling submitted by Wallace Laboratories.
August 20, 1996	Response to FDA telephone facsimile on August 14, 1996, requesting additional chemistry, manufacturing and control information and revised container labeling submitted by Wallace Laboratories.
September 18, 1996	Revisions to data submitted by Wallace Laboratories on August 20, 1996, re-submitted by Wallace Laboratories.
September 30, 1996	Response to FDA telephone facsimile on September 25, 1996, requesting additional chemistry, manufacturing and control information submitted by Wallace Laboratories.
October 9, 1996	Revised specifications submitted by Wallace Laboratories.
October 9, 1996	Safety Update submitted by Wallace Laboratories.
October 28, 1996	FDA method validation letter for NDA 20-114.
October 31, 1996	Revised product labeling submitted by Wallace Laboratories.
November 1, 1996	FDA notifying Wallace Laboratories that NDA 20-114 is approved.

#23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

07/551,644

In Re Patent of:	Helmut Hettche
Patent Number:	U.S. 5,164,194
Issued:	November 17, 1992
Expires:	November 17, 2009
FOR:	AZELASTINE CONTAINING MEDICAMENTS

Box Pat. Ext.
Commissioner of Patents and Trademarks
Washington, DC 20231

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. 156

Dear Sir:

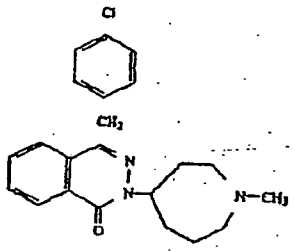
Applicant, Asta Medica, AG (formerly known as Asta Pharma, AG), represents that by virtue of an assignment recorded on December 26, 1989, at Reel 5237, Frame 0353, it is the assignee of the entire interest in and to Letters Patent of the United States No. 5,164,194 granted to Helmut Hettche. The claims of U.S. Patent No. 5,164,194 cover methods for using azelastine hydrochloride.

Pursuant to a license agreement dated August 16, 1982, Applicant granted Carter-Wallace, Inc., through its Wallace Laboratories Division, the exclusive right, with the right to grant sublicenses, to make, have made, use and sell the product azelastine in the United States of America together with the right to apply for, obtain and/or maintain investigational new drug exemptions ("IND's"), new drug applications ("NDA's") or other government clearances or approvals to market azelastine.

Azelastine hydrochloride NDA No. 20-114 which covers methods of using Wallace Laboratories' azelastine hydrochloride known as Astelin (hereafter the Approved Product) was approved on November 1, 1996.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. 156, providing the following information as required by 37 C.F.R. 1.740:

(1) The Approved Product has the following structure:



(2) The Approved Product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355), Section 505.

(3) Applicant's licensee received permission for the commercial marketing or use of the Approved Product under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on November 1, 1996.

(4) This application for extension of patent term of United States Patent No. 5,164,194 under 35 U.S.C. 156 is being submitted within the sixty (60) day period permitted for submission, the last day for said submission being December 30, 1996.

(5) The complete identification of the patent for which an extension is being sought is as follows:

Inventor:	Helmut Hettche
Patent No.:	U.S. 5,164,194
Issued:	November 17, 1992
Expiration Date:	November 17, 2009

(6) A copy of the patent for which an extension is being sought is attached herewith as "Attachment A."

(7) A copy of the receipt for payment of the 4 year maintenance fee is attached herewith as "Attachment B."

(8) No disclaimer, certificate of correction, re-examination certificate or other receipt of maintenance fee payment has been issued with respect to U.S. Patent No. 5,164,194.

(9) U.S. Patent No. 5,164,194 claims methods for using the Approved Product, as identified in paragraph (1) hereinabove. More specifically, the methods are claimed in claims 1-9 and 12 of U.S. Patent No. 5,164,194 as follows:

(1) A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

(2) A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically-acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

(3) A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

(4) A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

(5) A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

(6) A method as set forth in claim 1 in which the medicament is a solution.

(7) A method as set forth in claim 1 in which the medicament is an aqueous solution.

(8) A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

(9) A method as set forth in claim 1 in which the medicament is applied by spraying.

(12) A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the length of the applicable regulatory review period are as follows:

(a) U.S. Patent No. 5,164,194 was issued on November 17, 1992. U.S. Patent No. 5,164,194 is set to expire on November 17, 2009;

(b) IND for the Approved Product was filed by Wallace Laboratories on January 31, 1989, received and accorded IND No. 32,704 on February 6, 1989 and was effective on February 6, 1989;

(c) NDA for the Approved Product was submitted by Wallace Laboratories on March 26, 1991 (NDA No. 20-114); and

(d) NDA No. 20-114 for the Approved Product was approved on November 1, 1996.

(11) A brief description of the activities undertaken by the Applicant's licensee during the applicable regulatory review period with respect to the Approved Product and the significant dates applicable to such activities is attached herewith as "Attachment C."

(12) Applicant is of the opinion that U.S. Patent No. 5,164,194 is eligible for extension under 35 U.S.C. 156 because it satisfies the requirements for such extension as follows:

(a) 35 U.S.C. 156(a)
U.S. Patent No. 5,164,194 claims the method of using the Approved Product;

(b) 35 U.S.C. 156(a)(1)
The term of U.S. Patent No. 5,164,194 has not expired before submission of this application for extension;

(c) 35 U.S.C. 156(a)(2)
The term of U.S. Patent No. 5,164,194 has never been extended;

(d) 35 U.S.C. 156(a)(3)
The application for extension is submitted by the agent of the owner of record of U.S. Patent No. 5,164,194 in accordance with the requirements of 35 U.S.C. 156(d) and the guidelines of the U.S. Patent and Trademark Office;

(e) 35 U.S.C. 156(a)(4)
The Approved Product has been subject to regulatory review period before its commercial marketing or use;

(f) 35 U.S.C. 156(a)(5)(A)
The permission for the commercial marketing or use of the Approved Product, after the regulatory review period is the first permitted commercial marketing or use of the product, under the provisions of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred; and

(g) 35 U.S.C. 156(c)(4)
No other patent has been extended for the same regulatory review period for the Approved Product.

(13) The length of extension of the term of United States Patent No. 5,164,194 claimed by applicant is 349 days. The maximum allowable under 35 U.S.C. 156 (c)(3) since the addition of 349 days to the patent term would yield a patent term of 14 years from the date of approval of the Approved Product. The regulatory review period exceeds 349 days as shown by the following:

(a) The regulatory review period under 35 U.S.C. 156 (g)(1)(B)(i) and (ii) was from February 6, 1989 until November 1, 1996;

(b) United States Patent No. 5,164,194 issued on November 17, 1992, which was 1,380 days after commencement of the regulatory review period;

(c) The period of review "Testing Period" under 35 U.S.C. 156 (g)(1)(B)(i) was from February 6, 1989, until March 26, 1991, which is 779 days subject to the following limitation:

(1) deduction of 779 days which occurred on or before the issuance of United States Patent No. 5,164,194. Accordingly, zero days of regulatory review occurred during the "Testing Period".

(d) The period of review "Application Period" under 35 U.S.C. 156 (g)(1)(B)(ii) was from March 26, 1991, until November 1, 1996, which is 2046 days subject to the following limitation:

(1) deduction of 601 days which occurred on or before the issuance of United States Patent No. 5,164,194. Accordingly, 1445 days of regulatory review occurred during the Application Period.

(e) In the absence of the 14 year limitation imposed by 35 U.S.C. 156 (c)(3), noted above, the permissible period of extension of term of United States Patent No. 5,164,194 would have been 1445 days;

(f) In compliance with 35 U.S.C. 156 (c)(3) the period remaining on the term of United States Patent No. 5,164,194 after approval of the Approved Product 4748 days which when added to the 349 day extension claimed by applicant 5097 days is not in excess of 14 years and will give United States Patent No. 5,164,194 an expiration date of November 1, 2010.

(14) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to this application for extension.

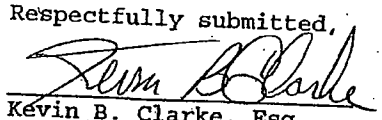
(15) The prescribed fee of $1090.00 for receiving and acting upon this application for extension is to be charged to Deposit Account 03-0935 as authorized in the accompanying letter which is submitted in duplicate. The requisite Declaration, set forth in 37 C.F.R. 1.740(a)(17) and (b) is also attached hereto.

(16) Inquiries and/or other correspondence relating to this application for patent term extension are to be directed to:

Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, New York 10105

(17) A certified duplicate copy of the application papers is submitted herewith.

Respectfully submitted,



Kevin B. Clarke, Esq.
Attorney for Applicant
Registration No. 22,647
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, New York 10105
(212) 339-5207

DEC 31 1996

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

#24

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Dear Mr. Wilson:

The attached application for patent term extension of U.S. Patent No. 5,164,194, was filed on December 18, 1996, under 35 U.S.C. § 156. U.S. Patent No. 5,164,194 issued on November 17, 1992 from an application that claimed priority to an application that was filed on November 9, 1988. Accordingly, the original expiration date of the patent is November 17, 2009.

The assistance of your Office is requested in confirming that the product identified in the application, Astelin, has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Telephone inquiries regarding this communication should be directed to the undersigned at (703) 306-3159.

Karin Tyson
Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Project

cc: Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY 10105

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DEPARTMENT OF HE_ _H & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

RECEIVED

FEB 21 1997

PATENT EXTENSION
A/C PATENTS

FEB 18 1997

Re: Astelin
Docket No. 97E-0014

#25

Stephen G. Kunin
Deputy Assistant Commissioner for
Patent Policy and Projects
Office of the Assistant Commissioner for Patents
U.S. Patent and Trademark Office
Crystal Park Building 2, Suite 919
Washington, D.C. 20231

Dear Mr. Kunin:

This is in regard to the application for patent term extension for U.S. Patent No. 5,164,194 filed by Astra Medica AG under 35 U.S.C. § 156. The human drug product claimed by the patent is Astelin (azelastine hydrochloride), which was assigned New Drug Application (NDA) No. 20-114.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in Glaxo Operations UK Ltd. v. Quigg, 706 F. Supp 1224 (E.D. Va. 1989), aff'd, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on November 1, 1996, which makes the submission of the patent term extension application on December 18, 1996, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the Federal Register, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely,

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs

cc: Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY 10105

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Re: Astelin

FDA Docket No. 97E-0014

#26

Dear Mr. Wilson:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 5,164,194. The application was filed on December 18, 1996, under 35 U.S.C. § 156.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term restoration. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Telephone inquiries regarding this matter should be directed to the undersigned at (703)306-3159.

Karin Tyson
Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

cc: Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY 10105

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Re: Astelin®
Docket No. 97E-0014

MAR 27 1997

RECEIVED #27
APR - 3 1997
PATENT EXTENSION
A/C PATENTS

The Honorable Bruce Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks
Box Pat. Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Commissioner Lehman:

This is in regard to the application for patent term extension for U.S. Patent No. 5,164,194, filed by Astra Medica AG, under 35 U.S.C. § 156 et seq. We have reviewed the dates contained in the application and have determined the regulatory review period for Astelin®, the human drug product claimed by the patent.

The total length of the regulatory review period for Astelin is 2,797 days. Of this time, 749 days occurred during the testing phase and 2,048 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: March 8, 1989.

   The applicant claims February 6, 1989, as the date the Investigational New Drug application (IND) became effective. However, FDA records indicate that the IND effective date was March 8, 1989, which was thirty days after FDA receipt of the IND on February 6, 1989.

2. The date the application was initially submitted with respect to the human drug product under subsection 505(b) of the Federal Food, Drug, and Cosmetic Act: March 26, 1991.

   FDA has verified the applicant's claim that the New Drug Application (NDA) for Astelin (NDA 20-114) was initially submitted on March 26, 1991.

3. The date the application was approved: November 1, 1996.

   FDA has verified the applicant's claim that NDA 20-114 was approved on November 1, 1996.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. § 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

for Stuart L. Nightingale, M.D.
Associate Commissioner
for Health Affairs

cc: Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY 10105

5,164,994

#28

(HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product MERETEK UBT™ Breath Test (urea, C–13). MERETEK UBT™ Breath Test is intended for use in the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the diagnosis of *H. pylori* infection in adult patients. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for MERETEK UBT™ Breath Test (U.S. Patent No. 4,830,010) from Meretekdiagnostics, Inc., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated February 21, 1997, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of MERETEK UBT™ Breath Test represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for MERETEK UBT™ Breath Test is 2,023 days. Of this time, 1,527 days occurred during the testing phase of the regulatory review period, while 496 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective:* March 7, 1991. The applicant claims January 19, 1990, as the date the investigational new drug application (IND) for MERETEK UBT™ Breath Test (IND 26,861) became effective. However, FDA records indicate that IND 26,861 was received by the agency on August 7, 1985. The protocol that first contained the Urea Breath Test was received by the agency on February 5, 1991, as part of this IND. Using February 5, 1991, as the beginning date plus adding 30 days for the receipt date of the modification, results in an effective date of March 7, 1991, for the testing phase of the active ingredient of this product.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and Cosmetic Act:* May 11, 1995. FDA has verified the applicant's claim that the new drug application (NDA) for MERETEK UBT™ Breath Test (NDA 20–586) was initially submitted on May 11, 1995.

3. *The date the application was approved:* September 17, 1996. FDA has verified the applicant's claim that NDA 20–586 was approved on September 17, 1996.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 780 days of patent term extension.

Anyone with knowledge that any of the dates as published is incorrect may, on or before June 3, 1997 submit to the Dockets Management Branch (address above) written comments and ask for a redetermination. Furthermore, any interested person may petition FDA, on or before October 1, 1997 for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (address above) in three copies (except that individuals may submit single copies) and identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 27, 1997.

Allen B. Duncan,

Acting Associate Commissioner for Health Affairs.

[FR Doc. 97–8625 Filed 4–3–97; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 97E–0014]

Determination of Regulatory Review Period for Purposes of Patent Extension; Astelin® Nasal Spray

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for Astelin® Nasal Spray and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Written comments and petitions should be directed to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Brian J. Malkin, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color

additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product Astelin® Nasal Spray (azelastine hydrochloride). Astelin® Nasal Spray is indicated for the treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in adults and children 12 years and older. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for Astelin® Nasal Spray (U.S. Patent No. 5,164,194) from Astra Medica AG, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated February 18, 1997, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of Astelin® Nasal Spray represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for Astelin® Nasal Spray is 2,797 days. Of this time, 749 days occurred during the testing phase of the regulatory review period, while 2,048 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective:* March 8, 1989. The applicant claims February 6, 1989, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was March 8, 1989, which was 30 days after FDA receipt of the IND on February 6, 1989.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and Cosmetic Act:* March 26, 1991. FDA has verified the applicant's claim that the new drug application (NDA) for Astelin® Nasal Spray (NDA 20–114) was initially submitted on March 26, 1991.

3. *The date the application was approved:* November 1, 1996. FDA has verified the applicant's claim that NDA 20–114 was approved on November 1, 1996.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 349 days of patent term extension.

Anyone with knowledge that any of the dates as published is incorrect may, on or before June 3, 1997 submit to the Dockets Management Branch (address above) written comments and ask for a redetermination. Furthermore, any interested person may petition FDA, on or before October 1, 1997 for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (address above) in three copies (except that individuals may submit single copies) and identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 27, 1997.

Allen B. Duncan,

Acting Associate Commissioner for Health Affairs.

[FR Doc. 97–8626 Filed 4–3–97; 8:45 am]

BILLING CODE 4160–01–F

National Institutes of Health

Pretesting of Office of Cancer Communications Messages; Proposed Collection; Comment Request

Summary: In compliance with the requirements of Section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, for opportunity for public comment on proposed data collection projects, the National Cancer Institute (NCI), the National Institutes of Health (NIH) will publish periodic summaries of proposed projects to be submitted to the Office of Management and Budget (OMB) for review and approval.

Proposed Collection

Title: Pretesting of Office of Cancer Communications Messages.

Type of Information Collection Request: EXTENSION (OMB # 0925–0046, expires 8/31/97).

Need and Use of Information Collection: In order to carry out NCI's legislative mandate to educate and disseminate information about cancer prevention, detection diagnosis, and treatment to a wide variety of audiences and organizations (e.g. cancer patients, their families, the general public, health providers, the media, voluntary groups, scientific and medical organizations), the Office of Cancer Communications (OCC) needs to pretest its communications strategies, concepts, and messages while they are under development. The primary purpose of this pretesting, or formative evaluation, is to ensure that the messages, communications materials, and information services created by OCC have the greatest capacity of being received, understood, and accepted by their target audiences. By utilizing appropriate qualitative and quantitative methodologies, OCC is able to (1) Understand characteristics of the intended target audience—their attitudes, beliefs and behaviors—and use this information in the development of effective communications tools; (2) produce or refine messages that have the greatest potential to influence target audience attitudes and behavior in a positive manner; and (3) expend limited program resources dollars wisely and effectively. *Frequency of Response:* On occasion. *Affected public:* Individuals or households; Businesses or other for

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 29 1997

#29

Re: Astelin®
Docket No. 97E-0014

Stephen G. Kunin
Deputy Assistant Commissioner for
Patent Policy and Projects
Office of the Assistant Commissioner for Patents
U.S. Patent and Trademark Office
Crystal Park Building 2, Suite 919
Washington, D.C. 20231

Dear Mr. Kunin:

This is in regard to the patent term extension application for U.S. Patent No. 5,164,194 filed by Astra Medica AG under 35 U.S.C. § 156. The patent claims the human drug product Astelin® (azelastine hydrochloride), New Drug Application (NDA) 20-114.

In the April 4, 1997 issue of the Federal Register (62 Fed. Reg. 16167), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before October 1, 1997, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely,

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs

cc: Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY 10105

JAN 2 8 1998

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY 10105

In Re: Patent Term Extension
Application for
U.S. Patent No. 5,164,194

#30

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 5,164,194, which claims the method of use of the human drug product ASTELIN®, is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 349 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Commissioner will issue a certificate of extension, under seal, for a period of 349 days.

The period of extension has been calculated using the FDA determination of the length of the regulatory review period published in the Federal Register of April 4, 1997 (62 Fed. Reg. 16,167). Under 35 U.S.C. § 156(c):

Period of Extension = ½ (Testing Phase) + Approval Phase
= (0) + 2,048 - 602
= 1,446 days

Since the regulatory review period began March 8, 1989, before the patent issued, November 17, 1992, only that portion of the regulatory review period occurring after the date the patent issued has been considered in the above determination of the length of the extension period. 35 U.S.C. § 156(c). The testing phase of an approved product is defined as the period beginning on the date that an exemption under subsection 505(i) of the Federal Food Drug and Cosmetic Act became effective for the approved product, March 8, 1989, and ending on the date an application for the approved product was initially submitted under subsection 505(b), March 26, 1991. Since both of these dates were before the issue date of the patent, none of the testing phase has been considered. The approval phase of a product begins on the date the application for the approved product was initially submitted. For ASTELIN®, this date was March 26, 1991, which was before the issue date of the patent, November 17, 1992. Accordingly, since from March 26, 1991 to November 17, 1992 is 602 days; this period is subtracted from the number of days occurring in the approval phase according to the FDA determination of the length of the regulatory review period. No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

However, the 14 year exception of 35 U.S.C. § 156(c)(3) operates to limit the term of the extension in the present situation because it provides that the period remaining in the term of the patent measured from the date of approval of the approved product (November 1, 1996) plus any patent term extension cannot exceed fourteen years. The period of extension calculated above 1,446 days, would extend the patent to November 2, 2013, which is beyond the 14 year limit (14 years after the approval date is November 1, 2010) set forth in 35 U.S.C. § 156(c)(3). Accordingly, the period of extension is the number of days to extend the term of the patent from its expiration date, November 17, 2009, to and including November 1, 2010, or 349 days.

The limitations of 35 U.S.C. § 156(g)(6) do not operate to further reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.	:	5,164,194
Granted	:	November 17, 1992
Original Expiration Date	:	November 17, 2009
Applicant	:	Helmut Hettche
Owner of Record	:	Asta Medica, AG
Title	:	Azelastine Containing Medicaments
Classification	:	424/489
Product Trade Name	:	ASTELIN® (azelastine hydrochloride)
Term Extended	:	349 days
Expiration Date of Extension	:	November 1, 2010

Any correspondence with respect to this matter should be addressed as follows:

By mail: Assistant Commissioner for Patents
Box Patent Ext.
Washington, D.C. 20231

By FAX: (703) 308-6916
Attn: Special Program Law Office

By hand: One Crystal Park, Suite 520
2011 Crystal Drive
Arlington, VA

Telephone inquiries related to this determination should be directed to the undersigned at (703) 306-3159.

Karin L. Tyson
Senior Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

cc: Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

RE: ASTELIN®
FDA Docket No.: 97E-0014

MAR - 2 1998

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

#31

Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY 10105

Re: Patent Term Extension
Application for
U.S. Patent No. 5,164,194

Dear Mr. Clarke:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 5,164,194 for a period of 349 days.

Telephone inquiries regarding this communication should be directed to the undersigned at (703)306-3159.

Karin Tyson
Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

cc: Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

RE: Astelin®
FDA Docket No.: 97E-0014

kt

US005164194A

United States Patent [19]

Hettche

[11] Patent Number: 5,164,194

[45] Date of Patent: Nov. 17, 1992

[54] AZELASTINE CONTAINING MEDICAMENTS

[75] Inventor: Helmut Hettche, Dietzenbach, Fed. Rep. of Germany

[73] Assignee: Asta Pharma AG, Fed. Rep. of Germany

[21] Appl. No.: 551,644

[22] Filed: Jul. 12, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 268,772, Nov. 9, 1988, abandoned.

[30] Foreign Application Priority Data

Nov. 13, 1987 [DE] Fed. Rep. of Germany 3738681

[51] Int. Cl.[5] A61K 9/14; A61K 31/55

[52] U.S. Cl. 424/489; 424/43; 424/45; 424/464; 424/422; 514/212

[58] Field of Search 424/43, 464, 422, 45, 424/489; 514/212; 222/394; 141/24; 239/302; 248/108

[56] References Cited

U.S. PATENT DOCUMENTS

158,564	1/1875	Barnes	141/24
2,119,643	6/1938	Mendl	222/394
2,136,940	11/1938	Ehbrecht	222/394
2,457,024	12/1948	Arp	248/108
2,995,308	8/1961	Ashkenez	239/302
3,813,384	5/1974	Vogelsang	546/133
4,704,387	11/1987	Engel et al.	514/212
4,769,369	9/1988	Thomas et al.	514/234.5

FOREIGN PATENT DOCUMENTS

2164058	7/1972	Fed. Rep. of Germany	546/133
3530793	3/1986	Fed. Rep. of Germany	514/212
1377231	1/1972	United Kingdom	

OTHER PUBLICATIONS

Negwer, Organic-Chemicals, Drugs and Their Synonyms, vol. II, (1987) p. 1145.

European Search Report.

Org.-Chem. drugs and their synonyms, vol. III, No. 6496 (1987).

Arzneimittel, Fortschritte 1972-1985, pp. 936 and 939 (1977).

Primary Examiner—Thurman K. Page
Assistant Examiner—Neil S. Levy
Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] ABSTRACT

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

12 Claims, No Drawings

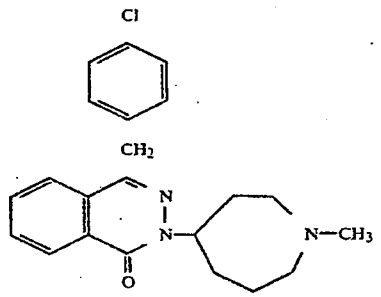
AZELASTINE CONTAINING MEDICAMENTS

This is a continuation of application Ser. No. 07/268,72, filed Nov. 9, 1988, now abandoned.

The present invention relates to the treatment of nasal and eye tissues with azelastine.

BACKGROUND OF THE INVENTION

Azelastine is a phthalazinone derivative having the following structural formula:



The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular for prophylactic treatment of asthma. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058.

SUMMARY OF THE INVENTION

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied directly in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste. The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of 1 : 706. This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions. It wa surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.

Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms.

A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissues.

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

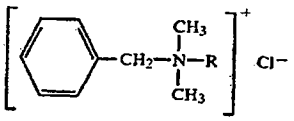
Through the use of nasal drops or a nasal spray, the dosage of azelastine required for the treatment of the cold is lowered approximately tenfold and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or syrups which distribute the active substance throughout the entire body. In the treatment of a banal illness such as a cold, a low incidence of side effects is particularly important and thus represents a considerable medical advance.

Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2- ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preserva-

tives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula C_nH_{2n+1}, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which $R=C_{12}H_{25}$ "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/ volume) of 2-phenylethanol.

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present-as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above. In the case of the eye drops, the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:

thimero sal 0.002–0.02%;

benzalkonium chlorie 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;);

chlorhexidine acetate or gluconate 0.01 to 0.02%;

phenyl mercuric/nitrate, borate, acetate 0.002–0.004%;

p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05–0.15, preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/-weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine components.

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50° to 0.56° C. is attained in comparison to pure water. In Example 1, for instance, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight-/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide and compressed air.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

When suspensions are used, the maximum particle size of the solid substances (azelastine +auxiliary substances) should not exceed 30 μm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 μm.

What occurs is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200,000 parts by weight of carrier substance (0.0005 to 2% of azelastine).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

EXAMPLE 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient

The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt. 2 H_2O, 68 g of sodium chloride, 1.25 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogen-phosphate. 12 H_2O as well as 10 g of hydroxypropylmethyl cellulose.)[1]

[1] Commercially available product, for example methocel E4M premium.

The solution obtained is diluted to 10.05 kg = 10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 μm after careful mixing, the first 500 ml of filtrate being discarded. The filtrate has a pH value of 6.8 ±0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

EXAMPLE 2

Nasal ointment with 0.1% of azelastine hydrochloride

5 kg of polyoxyethylene stearate[2], 8 kg of cetylstearyl alcohol (Lanette 0), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80° C.). Subsequently, a solution heated to 70° C. of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester in 51.021 kg of purified water are emulsified with the aid of a high speed stirrer and the emulsion obtained is stirred until cold and repeatedly homogenized at regular time intervals.

[2] Polyoxyethylene-40-stearate, solid, white to cream-colored mass, $D.^{25}$ ca. 1.1, F. 40°–44° C. Solidification point ca. 41° C.

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

EXAMPLE 3

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about −55° C. in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at −55° C. 0.0688 kg of micronized azelastine hydrochloride and 0.0688 kg of micron-

ized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about −55° C.

Following closure of the cooling vessel the suspension is again cooled to about −55° C. under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4

Eye drops with 0.05% of azelastine hydrochloride

140 g of polyvinylalcohol (trade name for example: Mowiol 26–88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90° C. and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium dihydrogen phosphate.2 H_2O and 21 g of disodium hydrogen phosphate.2 H_2O in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 μm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7. A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

* * * * *

J. BARNES.

Medicine-Droppers.

No. 158,564. Patented Jan. 12, 1875.

Fig. 1.

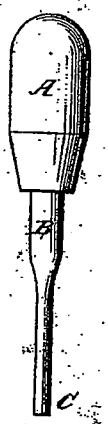


Fig. 2.

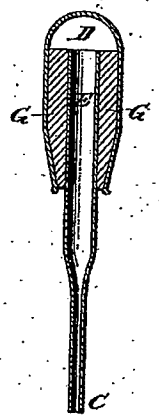


Fig. 3.

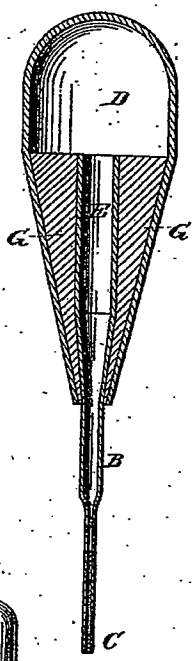


Fig. 4.

Fig. 6.

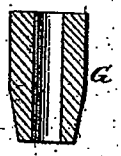
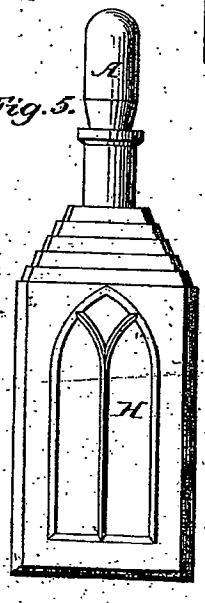


Fig. 5.



Witnesses.
C. G. Warren.
W. E. Barnes.

Inventor:
Joshua Barnes.

MP0174

UNITED STATES PATENT OFFICE.

JOSHUA BARNES, OF BROOKLYN, NEW YORK.

IMPROVEMENT IN MEDICINE-DROPPERS.

Specification forming part of Letters Patent No. **158,564**, dated January 12, 1875; application filed July 21, 1874.

To all whom it may concern:

Be it known that I, JOSHUA BARNES, of Brooklyn, in the county of Kings and State of New York, have invented a certain new and useful Improvement in Medicine-Droppers; and I do hereby declare that the following specification, taken in connection with the drawings forming a part of the same, is a clear, true, and accurate description thereof.

Pipettes have heretofore been so combined with bottle-stoppers that the contents of a bottle might be discharged drop by drop. In most instances these pipettes have been duplicated in one stopper or employed singly, and provided with a vent-passage, whereby air was permitted to enter the bottle as the fluid was discharged. No combined stopper and pipette of this class performs the true function of a stopper, as the continually-open pipettes admit of constant evaporation. Evaporation of a remedial solution gradually increases its power in proportion to the decrease of its bulk, and for that reason additional stoppers or caps have necessarily been employed, either for inclosing both of the pipette-apertures and the neck of the bottle, or for closing the two pipette-openings separately. Pipettes with a closed upper end and an open lower end have also been combined with stoppers, but in such, an opening has been provided, located about midway between the two ends of the pipe, or at least always below the stopper, in order that air may circulate in the pipette, and allow the liquid to freely enter at its lower or submerged end, and as freely to leave it in drops when removed from the bottle. In all of these forms of pipettes there exists a liability to clog internally, as the evaporated portion of the solution leaves a solid residuum therein.

My invention consists in providing the well-known compressible bulb and "pipette-dropper," with a bottle-stopper, whereby the pipette-tube may be charged with fluid to the extent of the last drop in the bottle, the dropper always maintained in a position ready for use, be protected by the bottle during intervals of use, the interior of the tube guarded against the introduction of air, and the liability of internally clogging the tube practically obviated.

Figure 1, the simple stopper in elevation in its customary form; Fig. 2, vertical section of the same; Fig. 3, vertical section of one adapted for bottles of several sizes; Fig. 4, stopper, with a bent tube that will take out the last drop in the bottle that it fits; Fig. 5, bottle in elevation, with the stopper applied; Fig. 6, vertical section of the cork, perforated to receive a tube, and before the india-rubber involucre is put on.

A, the india-rubber involucre; B, the glass or metallic tube; C, end of the tube, which, in some cases, would be quite small, as in the case of dispensing medicines drop by drop; D, the air-chamber; E, the reservoir of the tube; F, the curved end of the tube; G, the cork of the stopper; H, a bottle, to which the stop is adapted. The said stopper is made, first, by shaping a cork, and making through it a hole of the proper size; a tube is then put in, and over all an india-rubber involucre is put, the top of which extends above and leaves an air-chamber. (See Fig. 2.)

To extract liquor from any receptacle, the stopper is put in and the air-chamber pressed; then withdrawing the pressure the liquor flows up into the reservoir B of the tube. The stopper being withdrawn the liquor can be discharged from the tube in a stream, or by drops.

The stopper is best if made all of india-rubber, with the proper hole to receive the tube B.

If a cork be used, then the involucre of india-rubber need only partially cover it.

An important use of this when made large enough is to take samples of liquor from a cask or vat.

This invention is intended to be a practical bottle-stopper, as well as a medicine-dispenser, or dispenser of other fluids.

As already herein stated I am aware that it is not broadly new to combine a bottle-stopper with a medicine-dropper, but prior to my invention I know of no combined stopper and dropper, whereby the last drop in a bottle could be withdrawn; nor do I know of any pre-existing device of this character which would be a practicable one to employ in connection with compounded medicines put up in bottles and kept on sale. When tube-droppers, having a closed end, an open end, and a more or less centrally located vent, are em-

ployed, the vent, in the handling of the bottle and in placing it in different positions, is liable to, and does in practice frequently, get clogged by the solidification of matter in solution, requiring frequent clearance in order to admit fluid to the tube, or to discharge it therefrom. It is obvious that an open-mouthed dropping pipette would not have practicable value in this connection, as additional stoppers at each pipette would be requisite for the proper closure of the bottle. I am also aware that medicine-droppers have long been made and used, which were composed of a glass tube and compressible bulb, of the character herein described. These are extremely fragile, and are liable to be broken during intervals of use. Solid matter accumulates within said tubes during these intervals, as a result of evaporation of the solvent, and they are, therefore, not only liable to become clogged, but in practice are liable at times to discharge in a given number of drops a much greater quantity of the active matter than would be contained in the same number of drops in the original solution. This feature, under some circumstances, is liable to result in serious effects. By combining with the well-known pipe and compressible bulb a neck, which has the characteristics of a bottle-stopper, as herein described, the pipe may be inclosed in an empty bottle during intervals of use, and result in complete protection thereto, the bottle not only serving as a sheath or guard, but also as a means whereby the dropper may be maintained in a vertical position for effectual clearance from adhering matter, and also as a means for effectually secluding the dropper from the air and dust.

In practical use, my combined stopper and pipette is less liable to be forced from a bottle containing volatile matter than those which do not embody the compressible blub, for the reason that the readily-expanded vapors, induced by heat, instead of acting with direct pressure on the cork, are free to first exert themselves in expanding said bulb, which, in most cases, will relieve the cork from such a degree of direct pressure as would be liable to force it from the bottle if the bulb were not employed.

Having thus described my invention, I claim—

The combined stopper and drop-discharger, consisting of a dropping-tube, a compressible bulb, and a bottle-stopper, substantially as described.

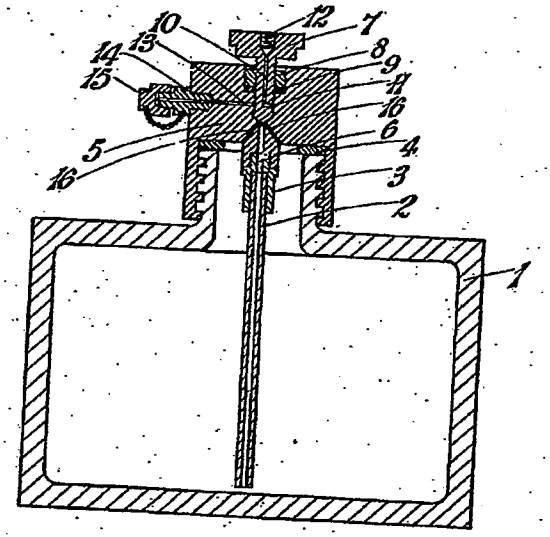
JOSHUA BARNES.

Signed in presence of—
A. G. WARREN,
W. E. BARNES.

June 7, 1938. V. MENDL 2,119,643

PRESSURE OPERATED DIFFUSER OF TOILET LIQUIDS

Filed Nov. 5, 1935



INVENTOR:
V. Mendl.
per George Hughes
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MP0177

Patented June 7, 1938 2,119,643

UNITED STATES PATENT OFFICE

2,119,643

PRESSURE-OPERATED DIFFUSER OF TOILET-LIQUIDS

Viktor Mendl, Prague, Czechoslovakia

Application November 5, 1935, Serial No. 48,345
In Czechoslovakia November 7, 1934

1 Claim. (Cl. 299—95)

This invention relates to spraying devices for use with bottles and like containers adapted to contain volatile liquid perfumes, eau de Cologne, lotions and the like.

The chief object of the invention is to provide a spraying device and container in which the liquid in the container is delivered in a finely atomized spray by the action of a gaseous pressure medium within the container and in which a finely adjustable valve device enables a quick and readily operated opening and closing of a supply conduit connecting the interior of the container to a mixing space with which also communicates a discharge passage and passages admitting some of the gaseous pressure medium to the mixing space to obtain a highly efficient atomizing action on the liquid as it leaves the supply conduit. Another object of this invention is to provide a spraying device with a single valve and seating.

In order that this invention may be clearly understood and readily carried into effect I have appended hereto a drawing showing in sectional elevation embodiment of the invention.

Referring to the drawing, the container is represented as a perfume bottle 1 having a threaded neck to which is affixed a closure cap 5, which effectively seals the bottle by means of a washer 4. An uptake tube 2 depends from the cap 5 and opens at its lower end near the base of the container 1, its upper end being sealed in a flanged and skirted cap 3 threaded into a central boss on the base of the cap 1. This cap 3 is bored in continuity with the bore of the tube 2 and with a central bore 6 in the cap 1.

The upper end of the bore 6 is normally sealed by the conical lower end of the screw 7, this screw having its thread tightly embraced by a packing ring 9 compressed by an annular collar or gland nut 8 threaded into a centrally tapped recess in the top of the cap 5.

The container 1 has a charge of compressed air or other suitable gaseous pressure medium in addition to its charge of liquid and consequently if the screw 7 is slightly rotated, e. g. by a milled head, some of the liquid in the container will be forced up the tube 2 and will enter the space in the cap 5 surrounding the now raised conical lower end of the screw 7. Debouching from this said space is a restricted outlet orifice 13 terminating at its outer end in a nozzle 14 fitted with a threaded closure cap 15, whereby liquid forced up the tube 2 will be to a certain extent atomized about the conical lower end of the screw 7 and will escape out through the nozzle 14 assuming the cap 15 is removed.

The atomizing action and rate of flow of the liquid are increased by providing one or more restricted passages 16 in the cap 5, extending upwardly and inwardly from the base of the cap to the conical seating formed inside the cap to receive the conical lower end of the screw 7 when it seals the passage 6. By this means the liquid and gaseous pressure medium are intimately mixed as they pass to the nozzle 14.

For the purpose of recharging the container 1 with compressed air or other suitable pressure medium a central bore 10 is formed in the screw 7 and the upper end of this bore is closed by a grub screw 12 having a conical lower end sealing the bore 10. The lower end of this bore 10 has a lateral outlet 11 communicating with the space surrounding the lower end of the screw 7, consequently if the grub screw 12 is removed, the screw 7 slightly raised and the cap 15 affixed an air compressor or pump can be connected to the cap 7 in place of the grub screw 12 and a further supply of compressed air can be admitted to the container 1.

By means of the present invention the spraying of a perfume or other liquid agent can be effected by a simple adjustment of the screw 7, and it is apparent that for a normally dimensioned scent bottle the milled head of the screw 7 can be manipulated by the forefinger of the hand holding the bottle.

What I claim is:—

Means for spraying scents comprising a receptacle containing the liquid scent and a gaseous pressure medium, a closure cap on said receptacle, a dispersion nozzle in said cap, a mixing space in said cap, a restricted conduit connecting the lower part of the interior of the receptacle to said mixing space, a number of restricted passages connecting the space in the receptacle charged with gaseous pressure medium to said mixing space, a valve in said mixing space, a valve seating common to the outlet ends of said restricted conduit and passages, said restricted passages being oblique in relation to the axis of travel of the liquid from said conduit to said mixing space, and means for operating said valve to adjust said valve to simultaneously connect said conduit and passages to said mixing space and also to connect said dispersion nozzle to said space, said valve and the means operating it comprising a screw with a conical valve head normally seated in the upper or outlet ends of said conduit and passages, a substantially axial bore extending along said screw to the top of the screw from a lateral opening above the conical head or end, and a threaded closure member in the top of said bore.

VIKTOR MENDL.

Nov. 15, 1938. A. EHBRECHT 2,136,940

ATOMIZER

Filed July 2, 1936

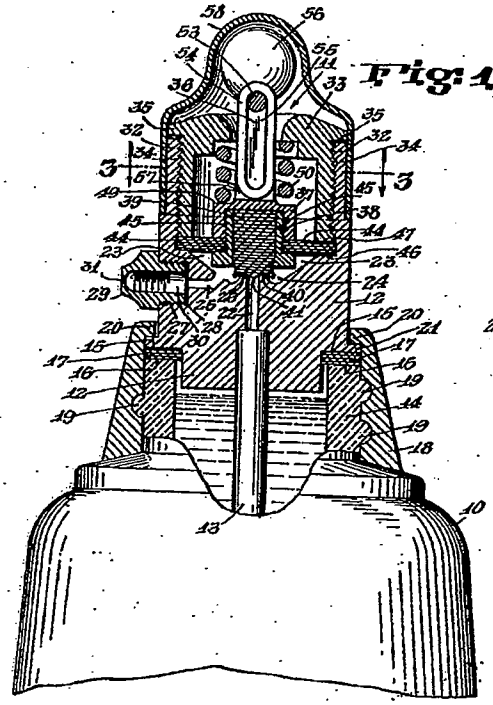

Fig: 1

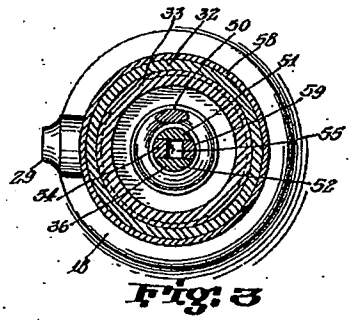

Fig: 3

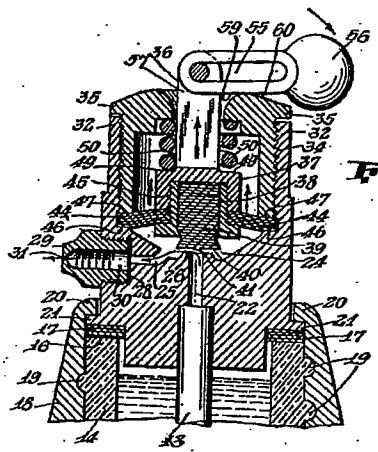

Fig: 2

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BY
by Donald Gibson
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MP0179

Patented Nov. 15, 1938 2,136,940

UNITED STATES PATENT OFFICE

2,136,940

ATOMIZER

Adolf Ehbrecht, New York, N. Y., assignor to The Aromel Corporation, New York, N. Y., a corporation of New York

Application July 2, 1936, Serial No. 88,582

1 Claim. (Cl. 299—95)

This invention relates to improvements in atomizers, particularly those applicable for use with perfumes or toilet waters.

Broadly, it is an object of this invention to provide an atomizer in which the liquid, be it perfume, toilet water, or other medium to be atomized, is under gas pressure, so that the discharge of the medium in atomized form is brought about through valve control.

Specifically, it is an object of this invention to provide a valve control for an atomizer, of the character described, wherein the valve is normally maintained in seated position with respect to the supply port through spring and diaphragm media; the port being opened upon displacement of the valve to permit pressure discharge in atomized form of the liquid, the spring and diaphragm media being adapted to return the valve to initial position for sealing the port upon release of the valve displacing mechanism.

Still further, it is an object of this invention to provide, in an atomizer of the character described, spring and diaphragm elements for maintaining the valve of the atomizer in seated condition with respect to a supply port, the diaphragm complementing the spring for returning the valve to seated condition, while at the same time serving as a seal for the chamber leading from the port to the discharge aperture of the atomizer.

These and other advantages, capabilities, and features of the invention will appear from the subjoined detailed description of one specific embodiment thereof illustrated in the accompanying drawing, in which

Figure 1 is a front elevation, partly in section, of the atomizer control in closed position.

Figure 2 is a front elevation, partly in section, of the open control.

Figure 3 is a plane view in section, taken along lines 3—3 of Figure 1.

Referring to the reference characters in the drawing, numeral 10 represents the base of the atomizer in the form of a container, herein shown of glass, though the same may be of metallic or non-metallic substance. The control mechanism 11 is carried on plug 12 from which extends syphon tube 13, leading interiorly of the base, the said plug 12 being carried on the wall 14 forming the neck of the base, there being disposed between the shoulder 15 of the plug and 16 of the base, gasket 17, of rubber or like material, the plug being locked to the base by means of cap 18, interiorly threaded to act on the exterior threads of the neck of the base, as at 19, said cap 18 having an inwardly extending rim 20 pressing against the annular rim 21 of the plug to form a firm lock between the plug and the base.

Within the plug 12 is formed a reduced bore or port 22 leading to delivery chamber 23, in which there is formed cup formation 24, leading to bore or discharge port 25, directed substantially at right angles to bore 23. A seat 26, of substantially annular form and projecting slightly above the base of chamber 23 surrounding the bore 22.

Within the side wall of plug 12 there is formed a threaded aperture 27, in which is disposed screen of fine mesh 28 and nipple 29, the screen being maintained in aperture 27 against the wall of the bore 25, by contact with the inner peripheral edge of the nipple thereagainst. The nipple 29 has bore 30 of gradually decreasing diameter leading to a substantial pin point 31 at its extremity, to provide the necessary atomizing nozzle.

Within wall 32 of the plug 12 there is carried the valve control mechanism 11 for the atomizer; said valve control mechanism comprising a head 33 having an exterior threading cooperating with the interior threading of the plug 12 as at 34, and having an annular rim 35 resting on the upper shoulder of wall 32 of the plug 12 to seal the same.

Within the head there is positioned a valve stem 36, the base of which comprises two interlocking sections, 37 and 38, the latter of which has firmly fixed therein valve 39 formed of rubber or like material, and having a flat base 40 resting against seat 26 surrounding bore or port 22, and having a teat 41 of diameter substantially to rest in bore or port 22. This flat formation 40 resting against the seat 26 and the teat 41 resting within bore 22, due to the resilient nature of the valve 39, forms a double seal for the supply outlet at port 22.

Between interlocking sections 37 and 38 there is disposed an annular diaphragm 44 formed, in this instance, of rubber, said annular diaphragm being locked between said sections at its inner periphery, and being maintained rigidly therebetween upon intermeshing of the threaded formation 45 of these members. The outer periphery of the diaphragm rests between rim 46 of the plug and shoulder 47 of the head, and is rigidly maintained in such position insofar as its outer periphery is concerned, through intermeshing of the threaded sections of said head and plug.

Mounted on valve stem 36 between the shoulder 48 of interlocking section 37, and inwardly ex-

tending annular groove 49 of the head 33, there is disposed compression spring 50, normally maintaining the valve stem and the valve structure carried thereby in position on seat 26 of the plug, for sealing the port 22. The valve stem 38, as shown in Figure 3, is bifurcated to provide arms 51 and 52, between which passes pivot pin 53, on which is mounted lever 54, having interior slot 55 and ball gripping portion 56, the lever 54 being of thickness equal to the width of the slot 57 between the furcations of the valve stem, so that it may be slid down therein when not in use. A cap 58, shown in Figures 1 and 3, is provided for sealing the device when not in use.

As shown in Figure 2, to operate the device the lever 54 is lifted upwardly, so that its end contacts with the pivot pin 53 of the valve stem, and so that one of its surfaces 59 presses against surface 60 of the head. When the ball 55 at the end of the lever is displaced in the direction of the arrow in Figure 2, with surface 60 of the head serving as the fulcrum valve stem 38 is moved upwardly in the direction of the arrow against the compression of spring 50 and against the resistance of diaphragm 44, causing a compression of spring 50 and annular displacement and distortion of the body portion of the diaphragm 44 in the direction of the arrow, thus placing the same under tension. By this action the valve 39 is displaced from its seat 26 and the teat 41 displaced from bore 22, permitting liquid medium contained within the base 10 to pass, by virtue of the gaseous pressure therein, through port 22, into chamber 23, to bore 25, through screen 28, into bore 30 of the nipple, and through the fine aperture 31 at the extremity thereof; the liquid under gas pressure, at the time it reaches the aperture 31, being, by virtue of its tortuous path, through reduced apertures, brought to a condition of fine atomization, as it strikes the air. When pressure against lever 54 is released, diaphragm 44 and spring 50 collectively tend to return to their original position, bringing valve 39 back onto seat 26, to seal the bore or port 22.

It is obvious that various changes and modifications may be made to the details of construction without departing from the general spirit of the invention as set forth in the appended claim.

I claim:

In an atomizer, a container for liquids to be sprayed, a conduit in the head of the container leading from the interior to an outlet thereof, a valve for sealing said conduit between the interior and the outlet, a coil spring acting axially, and a diaphragm acting peripherally of said valve to maintain the same in sealing position, and a lever attachable to one end of the said valve and adapted to be fulcrumed on the head of said container for displacing said valve against the action of said spring and diaphragm, said valve having a chamber in which said lever rests when not in use, the said lever having a slot and said valve a pin, whereby said lever may be displaced from the valve chamber for fulcruming action on the head of said container at right angles to said valve.

ADOLF EHBRECHT.

Dec. 21, 1948. C. ARP 2,457,024

COLLAPSIBLE TUBE HOLDER

Filed Feb. 13, 1945

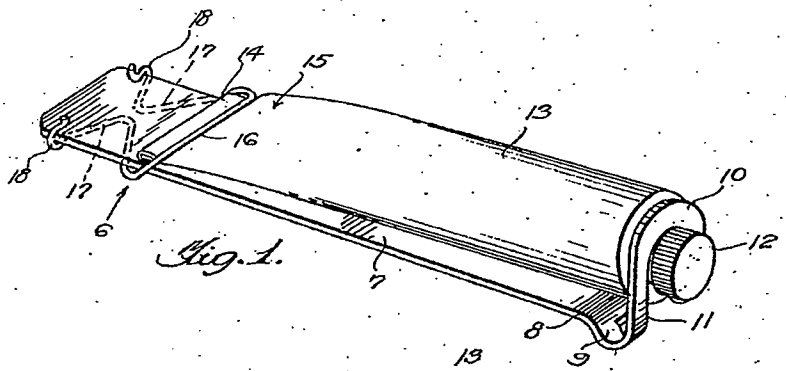

Fig. 1.

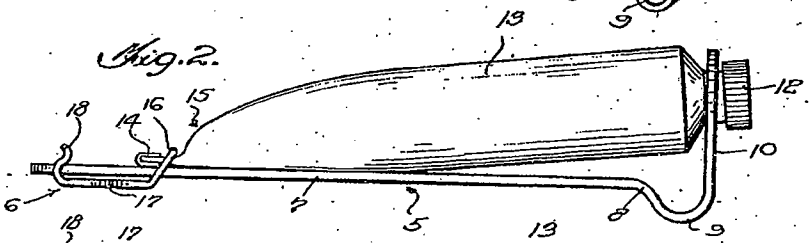

Fig. 2.

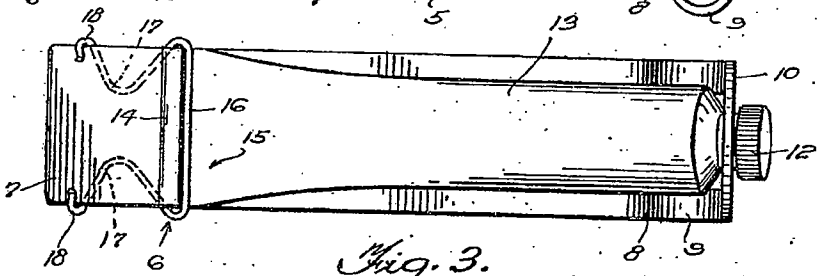

Fig. 3.

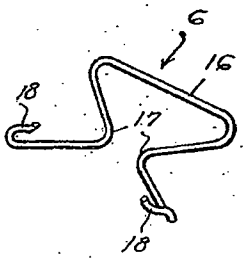

Fig. 4.

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